Association between the severity of nonalcoholic fatty liver disease and coronary artery calcification in postmenopausal women

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ABSTRACT

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Objective: Cardiovascular disease (CVD) is a leading cause of death in postmenopausal women. Nonalcoholic fatty liver disease is associated with CVD, however, little information is available regarding the relationship between CVD and NAFLD in postmenopausal women. The aim of this study was to investigate the relationship between the severity of NAFLD and coronary artery calcification (CAC), which is used as a marker of coronary atherosclerosis in postmenopausal women.

Methods: Out of 4,377 subjects who underwent a cardiac computed tomography (CT) in health promotion center between 2008 and 2013, 985 postmenopausal women were enrolled. Anthropometric profiles and multiple cardiovascular risk factors were measured. Severity of NAFLD was measured by ultrasonography and CAC was evaluated by cardiac CT.

Results: The subjects were stratified into three groups according to the severity of NAFLD. There were significant differences in cardiovascular parameters among the groups and the prevalence of CAC significantly increased with severity of NAFLD. In the logistic regression analysis after adjusted for multiple risk factors, increasing severity of NAFLD is significantly associated with CAC (odds ratio (95% CI), 1.40 (0.89-2.20) and 2.05 (1.24-3.39) ; P <0.05).

Conclusions: There was a significant association between the severity of

NAFLD and the prevalence of CAC, suggesting that NAFLD based on ultrasonography could be used as an independent marker for coronary atherosclerosis in postmenopausal women.

Key words : Nonalcoholic fatty liver disease, coronary artery calcification, postmenopause.

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I. INTRODUCTION

Nonalcoholic fatty liver disease (NAFLD) occurs in patients who do not consume alcohol, but shares similar histological features with alcohol-induced liver injury; ranging from simple steatosis to steatohepatitis, which can progress to advanced fibrosis and cirrhosis.[5] Previous studies found that the prevalence of NAFLD is more common in postmenopausal women than in premenopausal women[6], and the postmenopausal state has been suggested to be a risk factor for NAFLD.[6]

Nonalcoholic fatty liver disease is closely related to several metabolic disorders[7-9], and is also associated with an increased risk of cardiovascular disease (CVD), including coronary artery disease.[10] Recently, several studies have reported that NAFLD is associated with an increased incidence of cardiovascular events.[11-13]

CVD is a leading cause of death in postmenopausal women[1]. The coronary artery calcification (CAC), as measured by a multidetector computed tomography (MDCT), is a sensitive measurement to detect the existence of early coronary atherosclerosis. Moreover, the CAC may have prognostic value for predicting future cardiovascular events.[2-4]

However, few reports have examined the relationship between NAFLD and CAC, and the results of these studies were inconsistent [14-16]. Moreover, no

studies have investigated the relationship between CAC and the existence and severity of NAFLD in postmenopausal women.

Therefore, in this study, we investigated the relationship between the severity of NAFLD and the prevalence of CAC in postmenopausal women.

II. MATERIALS AND METHODS

Study population

This cross-sectional study included 4,337 individuals, all of whom visited the health promotion center in Gangnam Severance Hospital (Korea) between January 2008 and February 2013. Out of the 4,377 participants, postmenopausal women 50 years or older with no menstrual periods for more than 12 consecutive months and women with elevated FSH levels (>30) were included in this study. The exclusion criteria of this study included a history of excessive alcohol consumption (≥ 20 g/day), viral hepatitis (positive results for hepatitis B surface antigen or anti-hepatitis C virus), liver cirrhosis or malignancy as observed by ultrasonographic findings, or a past history of CVD. Ultimately, 985 postmenopausal women were enrolled in this study. The institutional review board of Yonsei University College of Medicine approved this study protocol, and written informed consent was obtained from all participants.

Clinical characteristics

Height and weight were measured, and the body mass index (BMI) was calculated by dividing the weight (kg) by the square of the height (m^2). Lifestyle, personal medical history of acute and chronic illnesses, and medication history were assessed using a standard questionnaire. Systolic and diastolic blood pressures were measured after a 5-minute rest. Patients with hypertension were defined as those who were taking antihypertensive agents, or who had a systolic BP of more than 140 mm Hg or a diastolic BP of more than 90 mm Hg. Patients with diabetes were defined as those who were taking glucose-lowering agents or had a fasting serum glucose level greater than 126 mg/dL.

Biochemical parameters

Blood samples were obtained from all participants after 12 hours of fasting. Glucose, aspartate aminotransferase (AST), alanine aminotransferase (ALT),

total cholesterol, high density lipoprotein cholesterol (HDL-C), triglyceride, and C-reactive protein (CRP) levels were determined by enzymatic methods using a Hitachi 7600-120 automated chemistry analyzer (Hitachi, Tokyo, Japan). Low density lipoprotein cholesterol (LDL-C) was calculated according to the Friedewald formula. Hepatitis B surface antigen levels and antibodies to hepatitis C virus were measured with a Roche E-170 device (Roche Diagnostics, Mannheim, Germany).

Ultrasonographic examinations

Diagnosis of fatty liver disease was based on an abdominal ultrasonography scan obtained with a 3.5-MHz transducer (HDI 5000, Philips, Bothell, WA, USA). Abdominal ultrasonographic examination was performed by one of three experienced radiologists, all of whom were blinded to the laboratory and clinical details of the subjects at the time of the procedure. Liver with any degree of fat accumulation was considered as NAFLD in the present study. The presence and severity of NAFLD was classified into one of three groups, according to the hyperechogenicity of the liver tissue, the degree of discrepancy between the liver and the right kidney, and the visibility of vascular structures. The three groups were: I, no fatty liver disease; II, mild fatty liver disease; and III, moderate to severe fatty liver disease.

CACS measurements with multidetector CT

Patient CACS were determined with a multidetector CT scanner (Philips Brilliance 64; Philips Medical System, Best, The Netherlands). We used a standard prospective ECG-gating protocol with a step-and-shoot technique. The scanning protocol included 64 x 0.625-mm slice section collimation, a 420-ms rotation time, a 120 kV tube voltage, and a tube current of 210 mAs[17]. Quantitative CACS were calculated with dedicated software and expressed as Agatston scores[17]. The presence of CAC was defined as a CACS > 0.

Statistical analysis

Data are expressed as means ± S.D. Intergroup comparisons were performed using ANOVA tests. Chi-square tests were used to compare categorical variables with percentages. Logistic regression analysis was used to analyze the association between the ultrasonographic severity of NAFLD and the prevalence of CAC (with a CACS > 0 as a marker of early atherosclerosis) while controlling for potentially confounding factors. The SPSS statistical package, version 20.0 (SPSS, Inc., Chicago, IL, USA) was used for all statistical analyses. *P* values < 0.05 were considered statistically significant.

III. RESULTS

A total of 985 subjects were included in this study. Of these, 779 subjects had no coronary artery calcification (CACS=0), whereas the remaining 226 exhibited some evidence of coronary calcification (22.9%). Of the subjects in this study, 339 were diagnosed with NAFLD via ultrasonographic data (34.4%).

The subjects were stratified into three groups according to the presence/severity of their fatty liver disease. Table 1 shows the demographic, clinical, and laboratory characteristics of the groups. Significant differences were observed in several metabolic parameters between the groups. Age, BMI, SBP, DBP, FPG, triglyceride, AST, ALT, and CRP increased according to the severity of fatty liver disease, whereas the HDL cholesterol decreased. The prevalence of diabetes mellitus and hypertension increased according to the severity of fatty liver disease.

The prevalence of CAC and the mean score significantly increased with the severity of fatty liver disease (Table 2, Fig. 1).

Logistic regression analyses were performed to determine the ORs for having a CACS > 0, according to the different severities of fatty liver disease (Table 3). When group I (no fatty liver disease) was set as a reference in unadjusted analyses, groups II (mild fatty liver disease) and III (moderate to severe fatty liver disease) had increased ORs for the prevalence of a CACS > 0. These relationships remained significant, even after adjusting for age and levels of SBP, DBP, BMI, FPG, total cholesterol, HDL cholesterol, LDL cholesterol, triglycerides, and CRP.

Table 1. Clinical characteristics of subjects according to the severity of their fatty liver disease

	I	II	III	*P* value
N	645	184	155	
Age (years)	57.2 ± 7.2	58.28 ± 6.1	59.5 ± 6.8	<0.01
BMI (kg/m^2)	22.1 ± 2.6	24.1 ± 2.8	26.0 ± 3.8	<0.01
SBP (mm Hg)	122.7 ± 18.4	127.8 ± 18.5	135.1 ± 19.4	<0.001
DBP (mm Hg)	75.1 ± 10.4	78.3 ± 10.2	81.3 ± 10.1	<0.001
FPG (mg/dl)	91.7 ± 13.5	99.4 ± 17.1	108.7 ± 27.7	<0.001
Total cholesterol (mg/dl)	200.8 ± 34.3	203.4 ± 34.4	205.1 ± 38.8	0.325
Triglycerides (mg/dl)	83.0 ± 38.8	115.0 ± 58.5	144.0 ± 80.3	<0.001
HDL cholesterol (mg/dl)	56.8 ± 12.9	51.1 ± 11.6	47.9 ± 9.3	<0.001
LDL cholesterol (mg/dl)	123.1 ± 31.0	127.2 ± 32.0	129.0 ± 36.6	0.064
AST (IU/L)	22.6 ± 9.0	24.2 ± 9.3	27.2 ± 12.0	<0.001
ALT (IU/L)	20.0 ± 11.6	25.5 ± 15.8	32.5 ± 19.2	<0.001
CRP (mg/L)	1.3 ±2.9	1.6 ± 2.4	2.2 ± 3.0	0.002
Diabetes (%)	3.1	10.3	17.4	<0.001
Hypertension (%)	21.5	30.4	41.9	<0.001

Data are represented as means ± SD. BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; FPG, fasting plasma glucose; LDL, low-density lipoprotein; HDL, high-density lipoprotein; AST, aspartate aminotransferase; ALT, alanine aminotransferase; gamma-GT, gamma-glutamyltransferase; CRP, C-reactive protein.

Table 2. Prevalence of subjects with CACS and means socre of ln(CACS+ 1) according to the severity of fatty liver disease

	I	II	III	*P* value
N	645	184	155	
ln(CACS+1)	0.6 ± 1.5	0.78 ± 1.6	1.1 ± 1.7	0.002
CACS >0 (%)	17.1	23.9	33.5	<0.001

CACS, coronary artery calcification score.

Table 3. Odds ratios and 95% confidence intervals for having a CACS > 0 according to the severity of fatty liver disease

	I	II	III	*P* value
Unadjusted	1	1.53 (1.03-2.28)	2.46 (1.66-3.64)	<0.01
Adjusted	1	1.40 (0.89-2.20)	2.05 (1.24-3.39)	0.02

Adjustments: age, BMI, SBP, DBP, total cholesterol, triglycerides, HDL cholesterol, LDL cholesterol, and CRP.

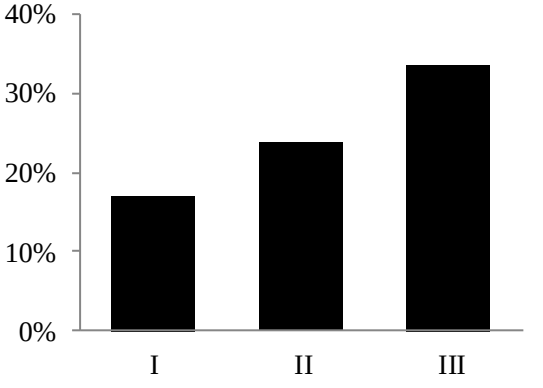

Figure 1. Prevalence of CAC (CACS > 0) according to the severity of fatty liver disease (*P* < 0.001).

IV. DISCUSSION

In this study, we investigated the relationship between between NAFLD and CACS in postmenopausal women and we found that this association was independent of CVD risk factors. To the best of our knowledge, this is the first study to demonstrate a correlation between NAFLD and the presence of a marker of early coronary artery atherosclerosis in postmenopausal women.

The prevalence of NAFLD in postmenopausal women in this study was 34.4%. This prevalence was higher than the prevalence of NAFLD in premenopausal women (19.7%), which was determined by analyzing the sub group comprised of premenopausal women out of this 4,377 participants. Hamaguchi et al[6] reported that the prevalence of NAFLD in Japanese postmenopausal women was higher than that in premenopausal women (15% vs 6%), and also concluded that postmenopausal state was a risk factor for NAFLD. Estrogen deficiency may play a role in these results. Estrogen has been shown to lead to the accumulation of gluteofemoral fat; moreover, the loss of estrogen during menopause is associated with an increase in central fat[1]. Hepatic estrogen receptors mediate estrogen action in the liver, and estradiol has been shown to play a favorable role in chronic liver disease[18]. Thus, estrogen appears to exert a protective effect against NAFLD in women[19].

Our data indicate that cardiovascular risk factors and the prevalence of DM and HTN increase with the severity of NAFLD. These results are supported by previous studies reporting an association between elevated levels of serum liver enzymes and the incidence of CVD[20,21].

The CACS has been shown to be an independent predictor of future cardiovascular events[22]; moreover, the importance of the CACS and its association with CVD is becoming increasingly recognized[17]. There are few reports of the association between NAFLD and the CACS, and the results of these studies were inconsistent. Some studies have suggested that NAFLD might be an independent risk factor for coronary artery disease[15,16]. However, a

cross-sectional cohort study of diabetes families in the Diabetes Heart Study found no significant associations between hepatic steatosis and coronary, aortic, or carotid calcium levels[14]. McKimmie et al suggested that hepatic steatosis is not likely to be a direct mediator of cardiovascular disease, and can be more accurately described as an epiphenomenon[14]. Until now, a causal relationship between NAFLD and coronary calcification has remained controversial.

Few reports have investigated the relationship between the severity of NAFLD and CAC. Lee et al[16] demonstrated that the severity of NAFLD correlated with metabolic abnormality, and was an independent predictor of CAC. However, this study was relatively small, consisting of only 342 subjects who did not consume alcohol. In our study, we found that the presence of coronary calcification (CACS > 0) increased with the severity of NAFLD in postmenopausal women. Importantly, this association was statistically significant, even after adjusting for cardiovascular risk factors.

The pathogenesis of NAFLD implies that lipids accumulate in hepatocytes, mainly as triacylglycerols[10]. Moreover, NAFLD, especially the necro-inflammatory form of NAFLD, may increase whole body insulin resistance and promote systemic inflammation through the release of proinflammatory and proatherogenic factors[10,23]. Other studies have shown that CRP, which is a known risk factor for CVD, is increased in patients with NAFLD, which may link NAFLD to coronary atherosclerosis[24,25]. In this study, we demonstrated that the level of CRP was elevated according to the severity of fatty liver disease.

There are a few limitations to our study. First, this is a cross-sectional study that cannot definitively establish causality. Thus, the precise causal relationship between NAFLD and CAC remains controversial. Second, this study was limited to a relatively racially homogenous group of Koreans who were enrolled at a single center. Finally, fatty liver disease was assessed by liver ultrasonography, a technique that cannot detect fatty infiltration below 30%[26].

The gold standard for assessing hepatic inflammation and fibrosis is histologic assessment using the Kleiner scoring scheme,[27] but this technique was not performed in this study. However, ultrasonography is nonetheless a very useful noninvasive technique that is often the first-line imaging technique in both clinical practice and epidemiological studies[28].

In conclusion, we demonstrated that an increased severity of NAFLD is significantly associated with CAC in postmenopausal women.

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ABSTRACT(IN KOREAN)

폐경 이후 여성에서 비알코올성 간질환의 정도와 심장혈관 석회화와의 관계

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김 민 경

연구목적: 심혈관 질환은 폐경 이후 여성에서 가장 많은 사망 원인이다. 비알코올성간질환은 심혈관 질환과 관계가 있는 것으로 생각되지만 폐경 이후 여성에서 정확하게 어떤 관계가 있는지에 대해서는 알려진 바가 적다. 그래서 폐경 이후 여성에서 비알코올성간질환의 정도가 심장혈관 동맥경화의 초기 지표인 심장혈관 석회화와 어떠한 관계가 있는지를 연구하고자 했다.

연구방법: 2008년부터 2013년까지 강남세브란스병원 건강검진 센터에 내원하여 심장혈관 전산단층촬영을 진행한 4,377의 수진자 중에, 985명의 폐경 이후 여성을 대상으로 분석하였다. 인체측정 및 혈액검사, 심혈관 질환의 위험인자에 대해서 조사하고 측정하였다. 비알코올성간질환의 정도는 초음파를 통해 측정하였고, 심장혈관 전산단층촬영을 통해 심장혈관 석회화를 측정하여 이를 분석하였다.

연구결과: 연구에 포함된 수진자들을 지방간의 정도에 따라 세 군으로 나누어 분석하였다. 심혈관 위험요소와 심장혈관 석회화의 존재는 각 군별로 의미있게 차이가 있었다. 비알코올성 질환의 정도는 심장혈관 석회화의 존재와 그 수치가 관계가 있는 것으로 보이고, 이는 다른 요인들을 교정하였을 때도 상관관계가 의미있게 유지되었다.

결론: 비알코올성 간질환의 심각한 정도와 심장혈관 석회화의 존재는

서로 관계가 있고, 이는 폐경 이후 여성에서 초음파로 측정된 비알코올성 간질환의 정도는 심장혈관 석회화의 독립적인 지표로 사용될 수 있을 것으로 생각된다.

핵심되는 말 : 비알코올성 간질환, 심장혈관 석회화, 폐경